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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/167,088	10/06/98	FINKELMAN	F 91830/625

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1641	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/167,088	Applicant(s) Finkelman et al.
	Examiner Gailene R. Gabel	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Oct 7, 1999*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-42* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-42* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Amendment Entry

1. Applicants' amendment filed October 7, 1999 is acknowledged and has been entered. Applicants amended claims 1, 8, 12, 20, 21, 22, 23, 25, 34, and 37. Currently, claims 1-42 are pending and under examination.

Claim Rejections - 35 USC § 112

2. Claims 1-42, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step (e) lacks **literal** antecedent support in reciting "the assay mixture of step d" because there is no literal recitation of an assay mixture in step (d). Reciting --in order to form an assay mixture-- after "targeting moiety:target analyte conjugate", or equivalent language in step (d), is suggested but not required to provide literal support for the assay mixture in step (e).

Claim 1, step (f), is indefinite in reciting "removing any unbound targeting moiety **from the capture moiety**" because as written, it appears to as if a "dissociation step" takes place between the targeting moiety:target analyte conjugate and the capture moiety after the "binding" step which is not what applicants intend. Furthermore, any unbound target analyte, should likewise be removed since the capture moiety in step (e) specifically binds the targeting moiety:target analyte conjugate. Reciting --removing any unbound and unconjugated targeting

moiety and target analyte from the assay mixture-- or equivalent language is suggested but not required to clarify the step.

Claim 1, step (g) provides for the use of one or more detection labels, but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 1, step (g) is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 1, step (h) is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, i.e. the "detection step" in step (g) and the "determination step" in step (h), such omission amounting to a gap between the necessary structural and functional connections. See MPEP § 2172.01. For example, is the amount of the target analyte that is determined related to the amount of targeting moiety:target analyte conjugate bound to the capture moiety that is detected.

Claim 12 provides for the use of a label, but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps

delimiting how this use is actually practiced. Language such as --wherein the targeting moiety is detectably labeled, wherein the label is selected from the group consisting of-- is suggested but not required to correct indefiniteness.

Claims 24 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim (claim 20 to which it depends upon). Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Furthermore, it is unclear as to whether the second targeting moiety to which the first targeting moiety is capable of binding is the capture moiety.

Claim 34 is indefinite and inconsistent relative to the method of claim 1 since claim 34 recites "A reagent kit... comprising (a) first reagent containing a ***labeled*** targeting moiety for the target analyte" whereas there is no clear recitation in claim 1 of the targeting moiety as being ***labeled***.

Claim 34 is indeterminate in scope by reciting "targeting moiety specific for the *target analyte*" and "contains the standard for the *analyte*" since the claim does not specifically identify the metes and bounds of the "target analyte".

New Matter

3. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, as amended, recites "injecting...an amount of neutralizing targeting moiety...at a concentration in excess of measurable quantities of secreted analyte" and points to page 18, lines 9-12, 22, and 23 and page 21 for antecedent basis. However, there is no literal support for this limitation in the specification, thereby rendering the claim as constituting new matter.

Claim Rejections - 35 USC § 103

4. Claims 1-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) in view of Finkelman et al. (Journal of Immunology 151: 1235-1244 (1993), and in further view of Pouletty et al. (US 5,612,034) for reason of record.

5. Claims 1-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) in view of David et al. (US 4,486,530) and Gosling (Clin. Chem. 36(8): 1408-1427 (1990)), in further view of Finkelman et al. (Journal of Immunology 151: 1235-1244 (1993), and in further view of Pouletty et al. (US 5,612,034) for reason as follows.

Tamarkin et al., Finkelman et al., and Pouletty et al. have been discussed in Paper No. 3.

Specifically, Tamarkin et al. disclose a competitive solid phase enzyme immunoassay for measuring the concentration of proteins, especially endogenous cytokines in the blood and other body fluids such as saliva, nasal secretions, tears and sweat if humans and animals. The

competitive solid phase immunoassay is a "one-site" immunoassay rather than a "sandwich" assay. Tamarkin et al. differs from the instant invention in failing to use a sandwich assay.

David et al. disclose a two-site or sandwich immunometric assay for determination of the presence and concentration of antigenic substances in fluids using monoclonal antibodies (see Abstract). David et al. specifically disclose unlabeled antibody bound to a solid support and at least one or usually two or more labeled monoclonal soluble antibodies carrying a fluorescing or quenching chromophobe, each antibody specific to a single antigenic site (see column 4, lines 51-68). Reverse and simultaneous immunometric assays can be conducted wherein a complex of labeled antibody:antigen will preclude formation of a complex between the antigen and antibody bound to the solid phase (see column 6, lines 54-68).

Gosling specifically teaches two-site "sandwich" assays which include assays involving labels in which all the principal reagents are used in excess. Gosling teach that the fundamental advantage in the performance characteristics of these assays are not dependent on antibody affinity as the competitive assays but rather specificity as determined by the combined selectivity of two antibodies, i.e. monoclonal antibodies. The most important variation of sandwich assays include the use of alternative labeling substances of antibody fragments to decrease non-specific binding (see page 1411).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teachings of Finkleman et al. in the stimulatory effects of injecting cytokine-anti-cytokine antibody complexes into the teachings of Pouletty et al. in administering binding

entities with active agents for the purpose of functionalizing proteins, and incorporate both teachings into the method of Tamarkin et al. using competitive solid phase immunoassay for measuring concentration of endogenous cytokines in order to obtain an accurate measure of in vivo production of cytokines in body fluids. One of ordinary skill in the art would have reasonable expectation of success in substituting sandwich immunoassay technique using labeled soluble monoclonal antibodies as taught by David et al. and Gosling into the competitive solid phase enzyme immunoassay as taught by Tamarkin et al. because David et al. specifically teach that sandwich immunometric assays are conventional and well-known in the art to be well-suited for the detection of polyvalent antigens using the combined selectivity of two antibodies as taught by Gosling and therein lies the motivation for one of ordinary skill in the art to substitute such method for its heightened sensitivity and accuracy through initial complexation of excess amount of labeled monoclonal antibodies with and specific for the target analyte. Furthermore, one of ordinary skill in the art would have been motivated to combine the teachings of both Finkelman and Pouletty for the purpose of enhancing in vivo production as well as extending in vivo life span of cytokines in order to to obtain a more accurate measure f such analyte level.

Response to Argument

6. A) Applicants argue that it is unclear how the cited references can be seen to provide the necessary specific motivation, much less a reasonable expectation of success, when none of the references address the problems which are solved by the present invention.

Contrary to applicants' contention, Tamarkin et al. recognize the need to obtain accurate measurements of various endogenous cytokines in body fluids independent of binding proteins. Finkelman et al. suggest that by conjugating cytokines with neutralizing anti-cytokine monoclonal antibodies the magnitude and duration of cytokine effects in vivo are increased, reflecting a more accurate measure of endogenous cytokine levels. Pouletty et al. recognize the need to maintain efficacy of (therapeutic) agents in bloodstream at extended periods of time and by linking a target to a long lived blood component (such as an anti-cytokine antibody as taught by Finkelman), a long lived depot of the target analyte is achieved. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Furthermore, see discussion commencing in paragraph 5.

B) Applicants argue that Tamarkin et al. reference is different from the instant invention in that it is a competitive assay using polyclonal antibodies adhered to a plate, it is not utilized in vivo to obtain the specific amount of analyte excreted over a fixed period of time, it does not teach using an excess of binding molecule, and it does not teach using a neutralizing molecule.

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some

teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Pouletty was incorporated into the teaching of Tamarkin et al. for his teaching that injecting long lived active agents, such as the neutralizing cytokine monoclonal antibodies as taught Finkelman et al., into the bloodstream for bonding to proteins creates a population of vascular functionalized long lived blood components. Furthermore and contrary to applicants argument, Tamarkin et al. uses polyclonal capture antibodies immobilized to a plate just as taught by the instant invention. Inasfar as immunoassays are concerned, Tamarkin et al. merely teaches a competitive form of ELISA for measuring endogenous cytokines in a biological fluid whereas other immunoassays such as sandwich assays are, likewise, conventional and well known and use of a particular assay would have been an obvious design choice as dependent upon its recognized diverse and specific advantages.

C) Applicants argue that Finkelman uses insufficient quantity of analyte binding molecule to sufficiently bind all the analyte, does not use excess binding molecules as that in the instant invention, does not provide necessary specific motivation much less a reasonable expectation of success that one could inject enough analyte binding molecule to allow analyte measurement but still less than the amount that would block natural immune response.

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some

teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, David et al. was incorporated therein for specifically teaching that two-site "sandwich" assays are well suited for polyvalent antigens such as the cytokines taught in the instant invention wherein Gosling teach that sandwich assays require excess amount of all principal reagents (labeled targeting moiety) because sensitivity is dependent on specificity between two antibodies. One of ordinary skill in the art would have reasonable expectation of success in substituting sandwich immunoassay technique as taught by David et al. and Gosling into the competitive solid phase enzyme immunoassay as taught by Tamarkin et al. because David et al. specifically teach that sandwich immunometric assays are conventional and well-known in the art to be well-suited for the detection of polyvalent antigens using the combined selectivity of two antibodies as taught by Gosling and therein lies the motivation for one of ordinary skill in the art to substitute such method for its heightened sensitivity and accuracy through initial complexation of excess amount of labeled monoclonal antibodies with and specific for the target analyte.

D) Applicants argue that Pouletty et al. merely point out a method of increasing the half-life of an injected compound that has a short in vivo half-life into an animal so that it binds covalently to a molecule that naturally has a long in vivo half-life wherein the half-life of the injected compound (not the endogenous compound) is increased. Applicants point to claim 8

wherein the paratopic molecules bind to endogenous compounds using noncovalent bonding, rather than covalent bonding.

Contrary to applicants' contention, Pouletty et al. teach that by linking a target to a long lived component (such as the anti-IL4 antibody as taught by Finkelman), a long lived depot of the target analyte is achieved (see column 2, lines 37-39). Inasfar as the paratopic molecules in claim 8, the claim has been amended to remove paratopic molecules as a limitation. Furthermore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. covalent/non-covalent bonding) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

7. In response to applicant's continuous arguments against the Tamarkin and other references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Tamarkin reference was used specifically in combination with Finkelman and Pouletty et al. Specifically, Tamarkin et al. disclose a competitive solid phase enzyme immunoassay and kit for measuring the concentration endogenous cytokines in a sample wherein cytokine is labeled by linkage with a binding partner conjugated to an enzyme or with fluorescent labels, radioactive elements, or luminescent labels. A polyclonal capture antibody which

recognizes many epitopes on the cytokine is adsorbed to a solid phase support to bind labeled cytokine wherein the amount of cytokine is determined. Finkelman was incorporated therein for his teaching that conjugating cytokine (IL-4) with neutralizing cytokine monoclonal antibody would increase in vivo activity greater than free cytokine because cytokine (IL-4) antibodies have a long in vivo half life. Finkelman et al. also specifically teaches that injection of cytokine and a neutralizing anti-cytokine monoclonal antibody at a molar ratio of 2:1 prolongs in vivo cytokine stimulatory activity and increases the magnitude and duration effects in vivo. Pouletty was incorporated therein for his teaching that injecting binding entities and active agents into the bloodstream for bonding to proteins and reacting to active functionalities of blood components creates a population of vascular functionalized blood components and by linking a target to a long lived blood component, a long lived depot of the target analyte is achieved. It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of both Finkelman and Pouletty in enhancing in vivo life span of cytokines with the solid phase enzyme immunoassay of Tamarkin et al. in order to obtain an accurate assessment of cytokine production as reflected by accurate endogenous cytokine measurements such as that in the instant invention. David et al. and Gosling references have been newly cited for their teaching of sandwich immunometric assays as conventional and well-known in the art to be well-suited for the detection of polyvalent antigens requiring use of excess amounts of principal reagents and as such used to substitute Tamarkin's method because of its heightened sensitivity

and specificity through use of labeled monoclonal antibodies which are specific for the target analyte.

In conclusion, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Finally, applicant's argument fails to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

8. Applicant's arguments filed 10/7/99 have been fully considered but they are not deemed persuasive.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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